

## **REMARKS**

### **I. Status of the Application**

Claims 1-36 are pending in the application. Claims 3-6, 15-17 and 26-36 have been canceled without prejudice to the filing of any appropriate continuation applications. Claims 1, 2, 7-14 and 18-25 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 1, 2, 7-14, 18-22 and 23-25 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chang et al. (1998) *Oncogene* 16:1921. Claims 7-9, 11-14 and 18-21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Levine et al., U.S. Patent No. 6,171,798 in view of Chang et al. Claim 10 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Levine et al. in view of Chang et al. further in view of Ts'o et al., U.S. Patent No. 5,962,237.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Support for the amendments can be found in the specification and the claims as originally filed. Specifically, support for the amendments to claim 1 can be found in the specification at least at page 2, line 25 to page 3, line 5. Support for the amendments to the claims to recite a human subject can be found in the specification at least at page 16, lines 8-10 and at page 20, lines 24-25. The remainder of the claims were amended to clarify claim language. The amendments presented herein add no new matter.

Applicants respectfully request entry and consideration of the foregoing amendments, which are intended to place the case in condition for allowance.

## **II. Formal Matters**

At page 2, paragraph 4 of the instant Office Action, the Examiner has noted that trademarks are recited in the instant application, and has requested that they be capitalized wherever they appear and that they be accompanied by generic terminology. In response, Applicants respectfully submit that the specification has been amended to incorporate trademark symbols as well as to capitalize the name of the mark.

## **III. Claims 1, 2, 7-14 and 18-25 Are Enabled**

At page 3, paragraph 6 of the instant Office Action, claims 1, 2, 7-14 and 18-25 stand rejected under 35 U.S.C. § 112, first paragraph, as not being reasonably enabled by the specification. The Examiner asserts that it would require undue experimentation to use Applicants' invention in a manner reasonably commensurate with the claims.

Applicants respectfully traverse this rejection. Applicants respectfully submit that the instant specification provides considerable direction and guidance on how to practice the claimed invention, which is directed to human subjects and involves a comparison between expression data of malignant oral tissue and normal oral tissue obtained from a single individual, using hybridization array technology.

Applicants have provided working examples which would enable one of skill in the art to practice the claimed invention. Applicants teach how to prepare nucleic acid samples (page 19, Example I), including use of a technique of separating normal cells from tumor cells from the same solid tumor site (page 19, line 19 to page 20, line 29). Applicants teach the analysis of nucleic acid samples using microarrays (page 21, lines 1-22). Applicants teach how to analyze

raw data obtained by microarray experimentation using software such as GENECHIP software, GeneCluster SOM and MATLAB<sup>TM</sup> (page 21, line 26 to page 25, line 25). Finally, Applicants teach that the expression of nucleic acids associated with oral cancer may easily be identified by comparing gene expression in normal cells vs. gene expression in tumor cells wherein the cells are obtained from the same individual. Applicants submit that although one of skill would have to compare the two cell types and determine gene expression levels, such experimentation would be routine and uses well known methods in the field. Such experimentation would not be undue.

Given the high level of skill in the art of cancer genetics at the time the instant application was filed, one of ordinary skill in the art, guided by Applicants' teachings, could easily practice Applicants' claimed invention without undue experimentation. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 7-14 and 18-25 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

#### **IV. Claims 1, 2, 7-14, 18-22 and 23-25 Are Definite**

At page 6, paragraph 8 of the instant Office Action, claims 1, 2, 7-14, 18-22 and 23-25 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants' regard as the invention. Applicants respectfully traverse this rejection of the claims as amended herein.

The Examiner asserts that claim 1 is indefinite because it is unclear as to how the recited steps of "contacting an array of probes with a population of amino acids" and "determining relative hybridization of the probes to the population" result in "monitoring expression of one or more genes associated with oral cancer in one or more cells," as recited in the claim preamble.

In response, Applicants have amended claim 1 to clarify the method steps, thus obviating this rejection.

The Examiner also asserts that claim 2 is indefinite over the recitation “the probes” because the claim previously refers to a “first array of probe” and a “second array of probes.” In response, Applicants submit that claim 1 was amended to recite a first array of probes and a second array of probes, thus obviating this rejection.

The Examiner further asserts that claims 7-14 are indefinite over the recitation of the limitation “the marker” in claim 7 because claim 7 refers to “at least one marker” and “group of markers” without reciting a single “marker.” In response, Applicants submit that claim 7 was amended to recite “a marker,” thus obviating this rejection.

The Examiner asserts that claims 11-14 are indefinite over the recitation of the limitation “the sample” in claim 11 because the claim recites multiple samples and it is unclear as to which of the samples constitutes “the sample” referred to. The Examiner also asserts that claims 11-14 are also indefinite over the recitation “the probes” in lines 7-8 of claim 11 because the claim recites a “first array of probes” and a second array of probes.” The Examiner asserts that claim 12-13 are indefinite over the recitation of the limitation “the nucleic acid” for having insufficient antecedent basis. The Examiner further asserts that claim 14 is indefinite over the recitation of “the array of probes.” In response, Applicants submit that claim 11 was amended to recite “a first array of probes,” “a second array of probes” and to refer specifically to a “test sample” and a “control sample.” Claim 14 was amended to recite “a first array of probes” and a second array of probes,” thus obviating the Examiner’s rejections.

The Examiner asserts that claims 18-21 are indefinite over the recitation of “the marker” and “the sample” because there is insufficient antecedent basis for these limitations. In response,

Applicants submit that claim 7 was amended to recite “a marker,” and claim 18 was amended to remove the language reciting “the sample,” thus obviating this rejection.

The Examiner asserts that claims 23-25 are indefinite over the recitation of “the sample” as claim 22 recites multiple samples. In response, Applicants submit that claim 22 was amended to recite “a first sample,” “a subsequent sample” and to refer to “the first and the subsequent samples,” thus obviating this rejection.

Accordingly, Applicants submit that the pending claims are definite. Therefore, Applicants respectfully request that the rejection of claims 1, 2, 7-14, 18-22 and 23-25 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

**V. Claims 1 and 2 Are Novel Over Chang et al.**

At page 9, paragraph 10 of the instant Office Action, claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Chang et al. (1998) Oncogene 16:1921. The Examiner is of the opinion that Chang et al. discloses methods in which the expression of genes associated with oral cancer are monitored by hybridization of nucleic acids from various types of cell samples with arrays of cDNAs expressed preferentially in HPV-immortalized cells. The Examiner further asserts that Chang et al. determines the relative binding of arrayed probes to the different population of nucleic acids, and identifies probes that are differentially expressed. Applicants respectfully traverse this rejection.

Applicants claims are directed to monitoring gene expression wherein the nucleic acids are derived from cells taken from *the same subject*. Comparing cells from the same subject is important because tumor samples from two individuals will not only correlate with differences between the states of the tumors, but with the *different physiological states of the individuals* as

well (specification, page 1, lines 26-29). By comparing genetic material from the same individual, Applicants' claimed invention enables the effective profiling of genes involved with oral cancer without the unpredictability that is typically present when comparing cell populations from different sources.

In contrast to Applicants' methods of expression monitoring cells derived from an individual, Chang et al. is directed to comparing gene expression patterns in oral cancer and HPV-immortalized oral epithelial *cell lines*. Chang et al. neither teaches nor suggests comparing gene expression patterns of cells taken from *a single human subject*, as claimed by Applicants.

The art cited by the Examiner illustrates variability obtained when attempting to compare oral cancer cells derived from different individuals or cell lines. Chang et al. teaches that there is "considerable cell line-to-cell line variability" (abstract) and that a "wide range of...factors such as cell culture conditions, cell proliferation rate and the effect of de-differentiation can affect gene expression" page 1921, right column. Chang et al. further states "expression profiles of three oral cancer cell lines were more *variable*" (page 1923, bottom of right column, emphasis added). Further, the Ibrahim et al. reference, cited by the Examiner, compares tumors from *different subjects* and teaches that "[t]he data showed *no statistically significant correlations* to tumour site, tumour grade, history of cigarette smoking and drinking of alcohol alone, or combined history of cigarette smoking and drinking of alcohol" (page 308, last paragraph, emphasis added). In contrast, Applicants' claimed methods enable one of skill to avoid variability inherent in different samples by comparing genetic material from normal cells and from tumor cells from the same patient.

Thus, Chang et al. fails to teach or suggest each and every element of the claimed invention. Accordingly, Applicants request that the rejection of claims 1 and 2 under 35 U.S.C. § 102(b) over Chang et al. be reconsidered and withdrawn.

**VI. Claims 7-14 and 18-21 Are Non-Obvious Over the Cited Art**

At page 10, paragraph 13 of the instant Office Action, claims 7-9, 11-14 and 18-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Levine et al., U.S. Patent No. 6,171,798, in view of Chang et al. The Examiner asserts that in view of the teachings of Chang et al., it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the method of Levine et al. so as to have employed the method in diagnosing oral cancers by detecting the levels of markers known to be differentially expressed in oral cancer in samples from a subject suspected of having oral cancer and comparing those levels to levels in normal controls. Applicants respectfully traverse this rejection.

Claim 7 and claims depending therefrom are directed to a method of diagnosing a human subject with oral cancer, the method comprising detecting the level of expression of a marker selected from a group of markers associated with oral cancer in a test sample from the human subject, and detecting the level of expression of the marker in a control sample from normal tissue from the human subject, wherein the level of expression of the marker in the control sample differs from the level of expression of the marker in the test sample when the subject is afflicted with oral cancer.

Levine et al. is directed to the identification of genes regulated by the protein p53. The Examiner admits that Levine et al. does not specifically teach detection of oral cancer, or teach the use in their method of cells obtained from oral tissue (section 13 of the instant Office

Action). Levine et al. does not teach or suggest comparing expression of a marker in a test sample and a control sample from the same subject, as claimed by Applicants. Chang et al. fails to cure the deficiencies of the primary reference for at least the reasons set forth above. Furthermore, neither reference recognizes the benefit of comparing samples derived from the same individual.

At page 11, section 14 of the instant Office Action, claim 10 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Levine et al., in view of Chang et al., further in view of T'so et al., U.S. patent 5,962,237. The Examiner asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Levine et al. and Chang et al. so as to have employed therein cells "obtained from blood cells" of the subject, and to have compared marker expression levels in such cells with levels in normal controls. Applicants respectfully traverse this rejection.

The combination of Levine et al. and Chang et al. fails to render the invention obvious for the reasons set forth above. T'so et al. fails to cure the deficiencies of the primary references. T'so et al. is directed to methods for enriching cancer cells from bodily fluid by multiple density gradient centrifugation. T'so et al. does not teach or suggest comparing expression of a marker in a test sample and a control sample from the same subject, as claimed by Applicants.

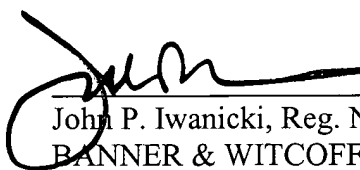
As none of the cited references teach Applicants' claimed invention, Applicants request that the rejection of claims 4-14 and 18-21 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

## VII. Conclusion

Having responded to all outstanding issues, reconsideration and allowance of the pending claims is respectfully requested. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-referenced application, the Examiner is urged to call the undersigned at (617) 720-9600.

Respectfully submitted,

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